

**BAKER BOTTS** LLP.Attorney Docket No.: A32011-A (072448.0313)  
PATENTREMARKS

This paper is being filed in response to the Office Action dated May 2, 2003, which issued in connection with the above-identified application. Claims 1-23 are pending. Claims 10-23 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) for being drawn to nonelected inventions following Applicants' election and traversal of the Restriction Requirement dated January 28, 2003. Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as allegedly being unpatentable over Kim et al., 1995, *Biotechnol. Prog.* 11(4):465-467 ("Kim") and U.S. Patent No. 5,552,086 to Siiman et al. ("Siiman"). Claims 5-9 are rejected under 35 U.S.C. § 102(b) as anticipated by, or alternatively under 35 U.S.C. § 103(a) as obvious over, both Kim and Siiman. Further, Claims 1-4 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kim in view of U.S. Patent No. 5,232,829 to Longiaru et al. ("Longiaru") as well as over Siiman in view of Longiaru.

The claimed invention is directed to an immunoassay system comprising bioassay plates having silver ions immobilized thereon. These plates are useful in immunoassays to specifically bind and detect antibodies or antigens. In particular, the claimed invention comprises a bioassay plate constructed of any material that can be functionalized to contain an amine group. Silver ions are added to the plate under conditions whereby the ions are immobilized on the plate. As a result of having silver ions embedded on the bioassay plate, biotinylated antibodies and antigens bind strongly to the silver-coated surface.

The Office Action alleges that Kim teaches "a device that comprises a support in which Ag(I) ions are immobilized" and upon which the "amino acids formed a complex with the silver ions." Kim presents a mathematical description of retention times for several amino acids

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on a polyacrylamide resin containing immobilized Ag(I) ions. The product taught by Kim expands immobilized, metal-affinity chromatography to include soft acid/soft base interactions. In attempt to equate the two inventions, the Office Action asserts that instant Claim 1 recites a "product" comprised of silver ions immobilized on a support. The Office Action admits, however, that the device in Kim "does not expressly disclose" that the support is in a plate format that comprises 96 wells. Furthermore, the Office Action alleges that Claims 5-9 are anticipated, or rendered obvious, by Kim.

The Office Action further states that Siiman discloses a device comprising a metal-coated polymer support that is in a bioassay, wherein the polymer includes polystyrene, and wherein the metal includes a silver salt. Siiman teaches a method for preparing stable colloidal particles having a thin coating of a selected metal that makes use of an aminodextran. Accordingly, this product advantageously enhances light scattering with excitation in the visible light region. Again, however, the Office Action admits that Siiman fails to teach a support in a plate format comprising 96 wells. The Office Action reiterates that, because Claim 1 recites a "product" comprised of silver ions immobilized on a support and Claim 2 recites a support comprising polystyrene, Siiman anticipates the present invention. The Office Action further alleges that Claims 5-9 are anticipated by, or rendered obvious over, Siiman.

The Office Action also alleges that Claims 1-4 are unpatentable over Kim in view of Longiaru, which teaches the synthesis of labeled target sequences of *Chlamydia trachomatis* using polymerase chain reaction (PCR). Longiaru further discloses detecting such sequences using a microtiter plate having a plurality of wells with a probe that is complementary to the target sequence. The Office Action asserts that it would have been obvious to one of ordinary

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skill in the art to combine the silver-containing polyacrylamide resin taught in Kim with the plate format of 96 wells as taught by Longiaru to achieve quicker assay time via a less labor-intensive assay design. The Office Action further alleges that Claims 1-4 are unpatentable over Siiman in view of Longiaru, proposing that it would have been obvious to one skilled in the art at the time of the invention to combine these two teachings as well.

**The Claims Are Not Anticipated**

To anticipate a claim, a reference must teach every element of the claim.

*Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."); *see also* M.P.E.P. § 2131.

Kim does not anticipate the claimed invention because Kim teaches a chromatography support (*i.e.* Bio-Gel P-2 polyacrylamide gel) and not a bioassay plate. The two supports are not at all alike, which is evidenced by the requirements for proper functioning of a bioassay plate that differ from a chromatography resin in many ways. For example, successful binding of a high concentration of biotin-labeled molecules that remain bioactive while on the surface of a bioassay plate is not taught or suggested by Kim. Also, procedures to avoid undesired binding of non-targeted molecules in the bioassay is not taught or suggested by Kim's work on chromatographic supports. Moreover, immobilization of silver ions on the bioassay plate of the instant invention does not change the important optical properties of the plate (*i.e.* the plate remains clear). In direct contrast, the chromatographic resin of Kim darkens in color, which indeed teaches away from maintaining optical properties that are instrumental to ELISA and other light-based detection methods widely used in plate-format bioassays. By simple virtue

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that a chromatographic resin is not a bioassay plate, Kim fails to teach every element of the claim, and consequently cannot anticipate the claimed invention.

Siiman similarly does not anticipate the claimed invention. Siiman discloses aminodextran compounds deposited on the surface of a colloidal size substrate to coordinate to and reduce metal salts or complexes to a metallic or metal(O) species which uniformly coat the surface of the aminodextran-coated colloidal substrate. Though Siiman provides that "[i]n the biotechnical and immunological examples given, solid, non-porous polymeric substrates [e.g. polystyrene] are preferred" (Col. 7, lines 31-34), the aminodextran (not the silver ion) is directly adsorbed to the surface of the substrate. Because aminodextran, and not silver metal or silver oxide, is used as the surface species, Siiman does not teach every element of Claims 1 and 2, and thus cannot anticipate the presently claimed invention.

**The Claims Are Not Obvious**

Three basic criteria must be met in order to establish a *prima facie* case of obviousness. First, there must be a suggestion or motivation to modify the references or combine their teachings. The fact that references *can* be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990); *see also* M.P.E.P. § 2143. Second, there must be a reasonable expectation of success. *In re Merck*, 231 U.S.P.Q. 375 (Fed. Cir. 1986). Third, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Only if all three of these requirements are met, can a *prima facie* case of obviousness be established.

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Claims 1-4 are not obvious over Kim in view of Longiaru because taken collectively, they teach away from the combination. Specifically, Kim uses its silver ion-bound support to separate amino acids by chromatography, which by its very nature employs weak binding interactions to differentially retard the movement of the different amino acids. The fundamental objective of chromatography is to rapidly separate molecules at high solvent-free purity levels. This is very different from the bioassay plates of the claimed invention, in which the silver ions that are immobilized on the bioassay plates strongly bind to biotinylated antibodies and antigens over a wide range of concentrations. Accordingly, the skilled artisan would not be motivated to modify the chromatography support described in Kim to achieve the claimed invention because the two models are premised on completely different modes of action (*i.e.* weak binding versus strong binding). Therefore, Kim and Longiaru teach away from the present invention, rebutting rejection of the claims based on obviousness.

The Office Action further proposes the combination of Siiman and Longiaru; however, these two references do not collectively provide suggestion or motivation to modify the references or otherwise combine the teachings. Siiman relates to colloidal particles employed in flow cytometry or Raman spectroscopy. In particular, Siiman teaches a method for preparing uniform colloidal particles coated with a thin metallic layer, preferably colloidal particles which have a thin, uniform peripheral coating of metallic gold or silver. Also taught is how to use such metal-coated colloidal particles as shifting agents in various instrumental methods, including flow cytometry and Raman spectroscopy. The skilled artisan would not be motivated to modify the colloidal particles of Siiman to obtain the claimed invention (*i.e.*, a silver-coated bioassay plate) because Siiman's intended purpose in no way suggests the claimed invention. There exists

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no motivation to combine these references and as a consequence, the Office Action fails to establish a *prima facie* case of obviousness.

In fact, the DYNATECH IMMULON plate disclosed in Longiaru is irradiated to provide increased binding affinity for hydrophilic complexes. Such treatment of the support creates indiscriminate reactive sites and results in haphazard immobilization of substrates, which is an undesired characteristic for a bioassay support because, *inter alia*, non-specific interactions are fostered and bioactivity of the captured molecules is unlikely to be preserved by this plate design. In contrast, the present invention provides binding selectivity in a relatively non-reactive background. Accordingly, Longiaru teaches away from the present invention.

The combination of Siiman and Longiaru also thus fails to teach a bioassay plate, and wholly separate from the lack of showing of motivation to combine these references, the Office Action fails to demonstrate that every limitation in each of Claims 1-4 is taught by the cited combination of references. Without a showing of each and every limitation in the proposed combination, a *prima facie* case of obviousness is not established.

The primary references relied upon (*i.e.*, Kim and Siiman) do not teach the use of a silver ions in a bioassay-plate-based system, indeed supporting Applicants' position that its claimed bioassay plate having silver ions immobilized thereon, and useful in immunoassays for specifically binding and detecting antibodies or antigens, was not at all obvious. *See, e.g., Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993); *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1318 (Fed. Cir. 2000) (reversing obviousness rejection involving technologically simple concept because there was no finding as to the principle or specific understanding within the knowledge of a skilled artisan that would have motivated the artisan to

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make the claimed invention); *In re Lee*, 61 U.S.P.Q.2d 1430, 1433-34 (Fed. Cir. 2002) (emphasizing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *Al-Site Corp. v. VSI Int'l Inc.*, 50 U.S.P.Q.2d 1161, 1171 (Fed. Cir. 1991) (the level of skill in the art cannot be relied upon to provide the suggestion to combine references); *see also* M.P.E.P. § 2143.01.

In fact, Applicants assert that the motivation to combine the cited references are not found within the teachings of the references themselves, and a combination to reach the claimed silver-coated bioassay plates was not in the knowledge of the ordinary skilled artisan. The Office Action's statements to the contrary are conclusory, and such statements imply impermissible hindsight reconstruction using Applicant's own teachings. Indeed, it is notable that prior to the filing date of the instant invention, use of silver ions in an aqueous solution containing phosphate or chloride ions in physiologically relevant concentrations was considered by skilled artisans to be unworkable due to the expected precipitation of the silver ions as silver chloride and/or silver phosphate. Accordingly, absent objective evidence that would motivate the skilled artisan to combine the cited references, or objective evidence that demonstrates a likelihood of success prior to the date of filing of the instant application, the Office Action fails to establish a *prima facie* case of obviousness. As such, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

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**Conclusion**

Applicants respectfully request reconsideration of the outstanding rejections as well as entry of the foregoing remarks into the file history of the above-identified application.

An early allowance is earnestly sought.

Respectfully submitted,

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